Public Health Goal for Thallium In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs).

Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR THALLIUM IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 0.0001 mg/L (0.1µg/L or 0.1 ppb) for thallium in drinking water. The current California Maximum Contaminant Level (MCL) is 0.002 mg/L (2 ppb) for thallium in drinking water. In the past, thallium was commonly used as a depilatory agent in humans until the toxicity of thallium was recognized. The PHG is based on a noncancer health endpoint observed in female rats administered thallium daily by gavage for 90 days (Stoltz et al., 1986). In this study, alopecia, or hair loss, was observed in both male and female rats which is a classic sign of thallium poisoning. This effect is consistent with other reports of the toxicity of thallium in both experimental animals and in humans. After critical analysis of the 90-day study data, it was determined by OEHHA that the incidence of alopecia in female rats at the highest dose of 0.25 mg/kg-day represented a biologically significant effect. Therefore, the no-observed-effect-level (NOEL) was identified to be the administered mid-dose level of 0.04 mg/kg-day. Of concern is the steep dose-response curve as extrapolated by comparing the results of the Stoltz et al. (1986) study with the results of two other subchronic exposure studies. In the two studies in which rats were administered higher levels of thallium in the diet for 15 weeks or in drinking water for 36 weeks, increased mortality was observed. The lethal doses were four to seven times higher than the highest dose used in the Stoltz et al. (1986) study. For the calculation of the PHG, a cumulative uncertainty factor of 3,000 was incorporated to account for the use of a subchronic study, uncertainty in inter- and intra-species extrapolation, and the steep dose-response curve. Based on these considerations, OEHHA derived a PHG for thallium in drinking water of 0.0001 mg/L (0.1 ppb).

INTRODUCTION

The purpose of this document is to develop a Public Health Goal (PHG) for thallium in drinking water. In this document, we evaluate the available data on the toxicity of thallium, with the primary focus on the literature related to oral exposures which may be most appropriate for the establishment of a PHG for drinking water. The studies which can be used to identify public health-protective levels are reviewed and summarized. The results of our evaluation are described below.

CHEMICAL PROFILE

Chemical Identity

Thallium is a naturally occurring metal represented by the chemical symbol Tl. The atomic mass of thallium is 204.383 and the atomic number is 81. Thallium occurs naturally as two isotopes, ^{203}Tl and ^{205}Tl, in a ratio of approximately 3:7 (WHO, 1996). In addition, there are 26 manufactured radioisotopes of thallium (Leonard and Gerber, 1997).

Physical and Chemical Properties

Thallium is a very soft and malleable heavy metal with a bluish-white color. It exists primarily in two valence states: monovalent (thallous) and trivalent (thallic). It is insoluble in water and soluble in nitric acid and sulfuric acid. It is highly reactive. When exposed to air and moisture, the surface of the metal oxidizes forming a coating of thallium oxide. In water, thallium hydroxide is formed. Thallium forms alloys with other metals and easily amalgamates with mercury. It also reacts with numerous compounds to form stable salts. (ATSDR, 1992; WHO, 1996) Properties of thallium, and a number of thallium compounds, are listed in Table 1.

Production and Use

Thallium is found ubiquitously in nature, however it occurs at low concentrations. The mean abundance of thallium in the earth's crust is estimated to be 1 ppm (HSDB, 1998). Thallium is not found in the elemental state in nature, but is present as a trace compound in many minerals, such as potassium, cesium, and rubidium. It is also found in sulfide ores of various heavy metals, including zinc, copper, iron, and lead (HSDB, 1998; WHO, 1996). Thallium has been detected in meteorites, volcanic rock and plants, and occurs in trace amounts in most living organisms. Minerals of thallium (crooksite, lorandite, hutchinsonite) have been found with thallium concentrations of up to 60%, but these minerals are very rare.

Thallium metal is obtained primarily from the byproducts of smelters. It is recovered from flue dust, from the residuals of smelting, or from the ores of lead, zinc, copper and iron. The production of thallium metal was discontinued in the United States in 1981 (HSDB, 1998; WHO, 1996; ATSDR, 1992).

Thallium sulfate was once used in medicine, primarily as a depilatory agent. However, therapeutic uses of thallium have been discontinued because of its toxicity. Since thallium is tasteless, odorless and highly toxic, there are many accounts of its use in homicides and suicides. Prior to the 1970's, thallium and various thallium compounds were used as pesticides for the control of rodents and insects. Use of thallium as a pesticide was banned in the United States in 1972. Today, thallium is used primarily in the semiconductor industry: alloyed with mercury, it is used in the manufacture of switches and closures which operate at subzero temperatures. In addition, thallium compounds are used in the manufacture of low-melting glass, electronic devices, mercury lamps, fireworks, and imitation gems. Thallium radioisotopes are used in medicine for scintigraphy of certain tissues and diagnosis of melanoma (HSDB, 1998; WHO, 1996; ATSDR, 1992; U.S. EPA, 1992b).

Sources

Thallium is released into the environment primarily from industrial processes in which thallium is a trace contaminant of the raw materials, rather than from facilities producing or using thallium compounds. Industrial sources of thallium include: combustion of fossil fuels, smelting operations (particularly of sulfide ores), cement manufacturing, and iron and steel production. It has been estimated that in the United States approximately 1000 tons of thallium are released into the environment each year (WHO, 1996; citing Schoer, 1984).

Table 1. Physical and chemical properties of thallium and selected thallium compounds[1].

Name	Chemical formula	Atomic/ molecular weight	Melting point (°C)	Boiling point (°C)	Solubility in water (g/L)
Thallium	Tl	204.38	303.5	1457	insoluble
Thallium acetate	$TlC_2H_3O_2$	263.43	131	-	very soluble
Thallium bromide	TlBr	284.29	480	815	0.5 (25°C)
Thallium carbonate	Tl_2CO_3	468.78	273	-	40.3 (15.5°C)
Thallium chloride	TlCl	239.84	430	720	2.9 (15.5°C)
Thallium fluoride	TlF	223.38	327	655	786 (15°C)
Thallium hydroxide	TlOH	221.39	139	-	259
Thallium iodide	TlI	331.29	440	823	0.006 (20°C)
Thallium nitrate	$TlNO_3$	266.39	206	430	95.5 (20°C)
Thallium (I) oxide	Tl_2O_2	424.77	300	1080	decomposes to TlOH
Thallium (III) oxide	Tl_2O_3	456.76	717	875	insoluble
Thallium sulfate	Tl_2SO_4	504.82	632	decomposes	48.7 (20°C)
Thallium sulfide	Tl_2S	440.85	448.5	-	0.2 (20°C)

[1] Sources: ATSDR (1992) and WHO (1996)

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Emissions of thallium into the atmosphere result primarily from coal-burning power plants, cement factories, and smelting operations (ATSDR, 1992). Thallium compounds are volatile at high temperatures and are not efficiently retained by emission control devices (WHO, 1996).

Data on thallium concentrations in ambient air are limited. One study reported a mean value of 0.22 ng/m^3 for North America. A study of six large cities in the United States reported a range of <0.04 to 0.1 ng/m^3. Thallium concentrations in Chadron, Nebraska were reported to range from 0.07 to 0.48 ng/m^3 in 1973 (WHO, 1996; citing Bowen, 1979; Ohnesorge, 1985; and Struempler, 1975). The thallium concentration near a coal-burning power plant was estimated to be 0.7 µg/m^3 (U.S. EPA, 1988).

Soil

Soil contamination by thallium occurs mainly from the solid wastes of coal combustion and smelting operations (Ewers, 1988; as cited by ATSDR, 1992). In the United States, thallium-containing wastes are now subject to U.S. Environmental Protection Agency (U.S. EPA) land disposal restrictions, therefore direct soil releases are likely to be small. However, soil contamination can occur as a result of dust fall-out in the vicinity of thallium emission sources. Soil samples from the vicinity of factories in Germany were reported to contain as much as 10 mg thallium/kg (ATSDR, 1992; WHO, 1996).

Water

Thallium contamination of water results from the many industrial processes previously mentioned (i.e., iron and steel manufacturing, mining, refining, and ore processing industries). Thallium concentrations in raw or treated waste waters from these industries have been reported to range up to 2 g/L. In 1987, total water releases from industrial sources were 1,850 pounds, as reported under U.S. EPA's Toxic Release Inventory (ATSDR, 1992). Thallium has been detected in urban waste waters, and both surface and ground water samples from hazardous waste sites.

Food

It has been suggested that food (particularly green vegetables) is probably the major source of thallium exposure (ATSDR, 1992). The thallium concentration in food is generally very low, with concentrations in plants less than 0.1 mg/kg dry weight. However, the thallium content of food depends directly on the thallium concentrations in the soil, therefore food grown in thallium-contaminated soils can be a significant source of thallium exposure (WHO, 1996; Leonard and Gerber, 1997). The World Health Organization (WHO, 1996), reviewing data from thallium-contaminated areas, found that the majority of fruits, vegetables, and meat contained

less than 1 mg thallium/kg fresh weight. Higher concentrations have been reported in cabbages, with up to 45 mg/kg reported in green kale. Thallium concentrations in the tissues of farm animals have been shown to correlate with concentrations in animal feed.

METABOLISM AND PHARMACOKINETICS

Absorption

Thallium is readily absorbed through various routes of exposure in both humans and experimental animals including rats, mice, and hamsters (WHO, 1996; U.S. EPA, 1992a and b); however, quantitative data regarding absorption estimates are extremely limited.

Thallium nitrate solution (^{204}Tl) administered to rats by six routes of exposure (oral, intravenous, intramuscular, subcutaneous, intratracheal, or intraperitoneal) was rapidly and almost completely absorbed by all routes tested (Lie et al., 1960). Following oral administration of thallium sulfate to one dog, at least 61.6% of the administered dose was absorbed based on measurements in urine (Shaw, 1933; as cited by U.S. EPA, 1992a and b).

No quantitative studies were located regarding absorption estimates in humans; however, several intoxication cases (e.g., following both oral and topical application of thallium compounds during depilatory treatment) and cases of human poisonings indicate that thallium can be absorbed through the gastrointestinal tract and through the skin (see U.S. EPA, 1992a and WHO, 1996 for reviews of these studies).

Distribution

Studies in mice (Andre et al., 1960), rats (Lie et al., 1960; Sabbioni et al., 1982; Downs et al., 1960), hamsters (Aoyama, 1989), rabbits (Talas and Wellhoner, 1983b and humans (Barclay et al., 1953; Talas et al., 1983a) indicate that thallium is rapidly distributed throughout the body, regardless of route of exposure. Highest concentrations are typically found in kidney. Thallium crosses the blood-brain and placental barriers. Studies in experimental animals indicate that transplacental transfer of thallium appears to be rapid and yields fetal concentrations that are lower than those observed in the mother (Ziskoven et al., 1983; Olsen and Jonsen, 1982).

Metabolism

Data on the biotransformation and the equilibrium between the valence states of thallium (Tl^{1+} and Tl^{3+}) in body fluids and tissues of mammals are not available (WHO, 1996; U.S. EPA, 1992a; U.S. EPA, 1992b). Results of a metabolism study in rats indicate that the two ions show a similar intracellular distribution (Sabbioni et al., 1980).

Excretion

Elimination of thallium may occur through the gastrointestinal tract, kidney, hair, skin, sweat and breast milk (WHO, 1996). In a study of a human cancer patient orally administered thallium sulfate (Barclay et al., 1953), excretion of thallium amounted to 15.3% in urine over 5.5 days,

and to 0.4% in feces over three days. In rats administered thallium sulfate by gavage, 32% of the dose was eliminated in feces and 21% in urine over an eight-day period following exposure (Lehmann and Favari, 1985). In rats administered thallium nitrate orally or parenterally, the ratio of fecal to urinary excretion of thallium ranged from two (on day two after dosing) to five (on day 16 following dosing) regardless of the route of administration (Lie et al., 1960).

The biological half-life of thallium in rats ranges from three to eight days (Lie et al., 1960; Lehmann and Favari, 1985). In humans, it has been estimated to be approximately 10 days, but values up to 30 days have been reported (Atkins et al., 1977; WHO, 1996).

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

The acute toxicity of water-soluble thallium compounds is similar for mice, rats, rabbits, hamsters and dogs (WHO, 1996). In general, LD_{50} values range between 20-70 mg Tl/kg bw for several routes of exposure (oral, subcutaneous, intraperitoneal, intravenous) (Stavinoha et al., 1959; Downs et al., 1960; Aoyama et al., 1988). The lowest oral doses of thallium compounds showing lethality are in the range of 5 to 30 mg Tl/kg bw for guinea pigs, rabbits and dogs (Downs et al., 1960).

Acute thallium toxicity in animals is characterized by the following: anorexia, vomiting, diarrhea, skin changes including hair loss, dyspnea and nervous disorders, and finally, respiratory failure leading to death (WHO, 1996).

Single subcutaneous injections of 20-50 mg thallium acetate/kg bw (15.5-38.8 mg Tl/kg) in rats produced mild to moderate enteritis, and moderate to severe colitis. Severe degenerative changes were found in mitochondria of kidney, liver, brain and small intestine (Herman and Bensch, 1967). Ultrastructural changes were also observed in liver mitochondria after single intraperitoneal injections of thallic chloride tetrahydrate in rats (doses of 26.7, 53.4 or 106.8 mg Tl/kg). Along with these mitochondrial changes, authors reported an increased number of autophagic lysosomes and structural changes in the endoplasmic reticulum of the liver (Woods and Fowler, 1986). Repeated subcutaneous injections in rats (two to three weekly injections of thallium acetate for up to 16 days; each injection 7.8-11.6 mg Tl/kg) produced ultrastructural degenerative changes in kidney and liver cells. In addition, lipofuscin bodies were present in neurons and acute necrosis was seen in mesencephalon tissue (Herman and Bensch, 1967).

In a study of thallium and kidney function, female rats were administered a single intraperitoneal injection of thallium sulfate (3.92, 7.98, 11.76, 15.68 mg Tl/kg bw) (Appenroth et al., 1995). Measurements taken 2, 5, and 10 days after a single administration of thallium sulfate revealed statistically significant changes in renal function (decreased glomerular filtration rate and urine volume, increased proteinuria) and renal morphology. The authors determined that the highest dose was nephrotoxic. All changes were reversible within the 10-day study period.

Weanling albino rats (five/group) were administered 2, 10, 50, 100, 500 or 5,000 mg thallium acetate/kg in the diet for one month. Exposure to 2 and 10 mg/kg caused no effects on growth and survival within the one month study period, whereas the other concentrations resulted in 60-100% mortality within 10 days (Downs et al., 1960).

Subchronic Toxicity

In a study conducted for U.S. EPA, thallium sulfate was administered daily by gavage to Sprague-Dawley rats (20/sex/dose) at levels of 0.01, 0.05, or 0.25 mg/kg bw-day for 90 days (Stoltz et al., 1986). Administered doses correspond to 8.1, 40.5 and 202.5 μg Tl/kg bw-day, respectively. Both untreated controls and vehicle controls were included in the study. At necrospy, the only grossly observed finding thought to be treatment-related was alopecia at the highest dose in female rats (Table 2). Among high-dose females, alopecia was observed in 12 rats. In 5 of those 12 female rats, alopecia was attributed to normal self-barbering behavior. In five others, the extent of alopecia was minimal (sporadic occurrence for one to seven days with the lowest severity ratings) and was attributed to normal cyclic pattern of hair growth. Two female rats exhibited moderate to severe alopecia that could not be attributed to self-barbering. Histological examination of skin samples from the high-dose females showed atrophy of hair follicles in these two rats. Upon final analysis, Stoltz et al. (1986) attributed the alopecia to the cyclic pattern of hair growth in rodents and concluded that the finding was "insignificant."

Aside from alopecia, moderate dose-related changes were observed in some blood chemistry parameters in both males and females (i.e., increased serum glutamic-oxaloacetic transaminase [SGOT], lactic dehydrogenase [LDH] and sodium levels; decreased blood sugar levels.) In addition, apparent treatment-related increases in the incidences of lacrimation and exophthalmos were observed throughout the study (Table 3). Opthalmic examination revealed no treatment-related abnormalities. No other treatment-related gross or light-microscopic findings were reported. Electron microscopy was not performed.

Table 2. Incidence of alopecia in rats exposed to thallium sulfate for 90 days[ab]

	total incidence of alopecia[c]	alopecia attributed to self-barbering behavior	alopecia attributed to normal cyclic hair growth	Possible treatment-related alopecia
female rats				
untreated controls	4	3	1	-
vehicle controls	1	0	1	-
0.008 mg/kg[d]	4	0	4	0
0.04 mg/kg	9	5	4	0
0.2 mg/kg	12	5	5	2
male rats				
untreated controls	2	0	2	-
vehicle controls	1	0	1	-
0.008 mg/kg	4	2	2	0
0.04 mg/kg	9	6	3	0
0.2 mg/kg	4	0	4	0

[a] n = 20 animals/sex/dose
[b] source: Stoltz et al., 1986
[c] number of animals observed with alopecia at least once during the 90-day study (for alopecia attributed to normal cyclic hair growth, the frequency of occurrence was usually less than 10 days).
[d] administered doses provided, target doses were as explained in the text.

Table 3. Clinical observations in rats treated with thallium sulfate for 90 days [ab]

	untreated controls		vehicle controls		0.008 mg/kg dose group[c]		0.04 mg/kg dose group		0.2 mg/kg dose group	
Observation	M	F	M	F	M	F	M	F	M	F
Eyes:										
Lacrimation	1	7	7	6	20	20	20	20	20	20
Exophthalmos	1	5	5	6	13	19	20	20	20	20

[a] number of animals observed with the effect at least once during the 90-day study; 20 animals per group.
[b] source: Stoltz et al., 1986
[c] administered doses provided, target doses were as explained in the text.

In another study (Downs et al., 1960), male and female weanling Wistar rats (five/sex/dose; each weighing 0.05-0.08 kg) were administered 0, 5, 15 or 50 mg thallium acetate/kg in the diet for 15 weeks. Two groups of rats, added to the study later, were fed diets containing 0 or 30 mg thallium acetate/kg feed for 63 days. Mortality was high among control and test animals. Among animals on the 15-week protocol, mortality was 40% in the control group (two animals/sex), while mortality in treated animals was 20%, 40% and 100%, respectively. Of the animals in the highest dose group (50 mg thallium acetate/kg diet), all males died by the second week of the study, and all females died by the eighth week of the study. In the groups added to the study, mortality was 30% (controls) and 80%, respectively. At necropsy, moderate to marked alopecia was reported in rats fed 15 and 30 mg thallium acetate/kg diet. The authors noted that the hair loss was first observed after two weeks of treatment and by termination the rats were almost hair free. No histopathological changes were reported in any organs examined, although skin sections were not prepared. The exact concentrations of thallium ingested by the rats were not determined, however Downs et al. (1960) estimated consumption to be in the range of 1 to 3 mg thallium acetate/kg bw-day (0.78 to 2.34 mg Tl/kg bw-day) for diet containing 15 mg thallium acetate/kg diet. Using U.S. EPA's approach, if it is assumed that a 100 gram young rat consumes 10 grams diet per day, administered doses (0, 5, 15, 30 or 50 mg Tl acetate/kg_{diet}) correspond to approximately 0, 0.4, 1.2, 2.4 or 3.9 mg Tl/kg bw-day (U.S. EPA, 1992a and b). The authors did not provide an explanation for the high mortality among control animals.

In a similar study by the same authors (Downs et al., 1960), Wistar rats (five/sex/group) were administered 0, 20, 35, 50, 100 or 500 mg thallium oxide/kg in the diet for 15 weeks. Using U.S. EPA's assumptions as above, administered doses correspond to approximately 0, 1.8, 3.1, 4.5, 9.0 or 44.8 mg Tl/kg bw-day.) All animals of the three highest dose groups died within eight weeks of treatment. Mortality rates among the other groups were as follows: 20% (controls), 20% and 60%, for the two lower dose groups, respectively. Alopecia was observed in all dose groups. Necropsy of the surviving animals showed a statistically significant elevation in kidney weights of females fed 20 and 35 mg thallium oxide/kg diet, and males fed 20 mg thallium oxide/kg diet. Histological examination of skin sections revealed a marked decrease in the number of hair follicles and hair shafts. The authors also reported finding considerable atrophy of the remaining hair follicles and of the sebaceous glands. The epidermis was found to be keritinized, and in some cases the follicles were cystic. Apparently, follicles were being replaced

by scar, collagen or fat. The changes in skin were compared to changes observed in atrophic scleroderma. No histological changes were observed in lungs, liver, kidneys or brain.

Thallium sulfate was administered in drinking water to 80 female Sprague-Dawley rats for 36 weeks (Manzo et al., 1983). The concentration of thallium in the water was 10 ppm. Authors reported a total intake as high as 80 mg thallium/rat, or approximately 1 mg Tl/kg-day. Twenty-one percent of the animals died before the end of the study. Thallium exposure resulted in mild to severe cutaneous disorders. A 20% incidence of alopecia was reported, with some rats losing almost all hair by the end of the exposure period. Abnormal electrophysiological parameters (e.g., reduced amplitude of motor and sensory action potentials) were measured in 10 of 16 rats following 240 days of exposure. Morphologic changes were found in sciatic nerve samples from three of six thallium-treated rats.

Fifteen Sprague-Dawley rats were administered thallium acetate subcutaneously. An initial injection of 10-20 mg/kg (i.e., 7.8-15 mg Tl/kg) was followed by weekly injections of 5 mg/kg (3.9 mg Tl/kg) for up to 26 weeks. Occasionally, one or two injections were reduced or withheld due to signs of toxicity. Physical signs of toxicity in treated animals included: failure to gain weight, hair loss and poor hair luster, diarrhea, conjunctivitis, irritability, dragging of hind limbs. Although ultrastructural changes were not visible with light microscopy, electron microscopy revealed mitochondrial damage in kidneys and liver, and lipofuscin bodies in brain neurons (Herman and Bensch, 1967).

Genetic Toxicity

Few studies have been performed on the genotoxicity of thallium. The evidence of mutagenic effects is limited at this time (WHO, 1996; Leonard and Gerber, 1997); however, there are data suggestive of DNA strand breaks. Reverse mutation assays in *Salmonella typhimurium* and *Escherichia coli* were negative (Claussen et al., 1981; Kanematsu et al., 1980). In addition, no statistically significant increases in sister-chromatid exchange were observed in bone marrow cells after oral administration of thallium chloride to Chinese hamsters (5 or 10 mg thallium/kg bw; two doses in a 24-hour period) (Claussen et al., 1981). Incubation with thallium carbonate (10^{-4} to 10^{-6} M) caused a dose-related increase in strand breaks in C57BL/6 mouse embryo cells, CBA mouse embryo cells, and rat embryo fibroblasts (Zasukhina et al., 1981; Zasukhina et al., 1983). Thallium was positive in a rat dominant lethal assay (Zasukhina et al., 1983); however, the significance of the results for health risk assessment are difficult to assess due to incomplete reporting of both the results and the protocol (U.S. EPA, 1992b).

Developmental and Reproductive Toxicity

In a reproductive toxicity study (Formigli et al., 1986), groups of 10 male Wistar rats were given 10 ppm thallium in drinking water for 30 or 60 days (approximately 740 μg/kg bw-day). After 30 days of exposure, no adverse effects were observed. Rats exposed for 60 days, however, exhibited adverse effects on sperm cell maturation and motility. Histological examination revealed alterations in the epithelium of the seminiferous tubules, as well as ultrastructural changes in Sertoli cells. The activity of β-glucuronidase, an enzyme primarily located in the Sertoli cells, was significantly reduced; other biochemical markers of testicular function were not different from that of controls.

In a study of female Wistar rats, thallium acetate or thallium chloride was administered by gavage at doses of 0, 3, 4.5 or 6 mg/kg on days 6 through 15 of gestation. Administered doses correspond to 0, 2.3, 3.5 and 4.7 mg Tl/kg-day for thallium acetate, and 0, 2.6, 3.8 and 5.1 mg Tl/kg-day for thallium chloride. The two highest exposure concentrations of both the acetate and the chloride resulted in 100% mortality in the dams. Exposure to 3 mg/kg of either compound resulted in increased malformations of the ribs and vertebrae in the pups, as well as a slight increase in postnatal mortality (Claussen et al., 1981; as summarized by WHO, 1996; U.S. EPA, 1992a; and U.S. EPA, 1992b).

In a parallel study, pregnant NMRI mice were administered 0, 3 or 6 mg/kg thallium acetate or thallium chloride by gavage on days 6 through 15 of gestation. Administered doses correspond to 0, 2.3 and 4.7 mg Tl/kg-day for thallium acetate, and 0, 2.6 and 5.1 mg Tl/kg-day for thallium chloride. In animals receiving thallium chloride, no adverse effects were noted at 3 mg/kg. At 6 mg/kg there were slight increases in postimplantation loss and postnatal mortality. In animals receiving thallium acetate, adverse effects were reported at both exposure concentrations. Incidences of cleft palate were slightly increased at both 3 and 6 mg/kg. In addition, lower fetal weights were noted at 6 mg/kg (Claussen et al., 1981; as summarized by WHO, 1996; U.S. EPA, 1992a; U.S. EPA, 1992b).

Rat pups, one-day-old, were given single intraperitoneal injections of thallium acetate (16 mg Tl/kg) and monitored for 50 days. In general, thallium-treated animals were smaller in size, and showed progressive muscular atrophy. Histological examination revealed severe and progressive alterations in peripheral nerves and muscle (Barroso-Moguel et al., 1996).

Noncancer Chronic Toxicity

No chronic animal studies on the toxicity of thallium were located.

Carcinogenicity

No studies on the carcinogenicity of thallium in animals were located.

Toxicological Effects in Humans

Acute Toxicity

In adults, oral lethal doses of thallium are estimated to range between 6 and 40 mg/kg, with an average dose of 10-15 mg/kg (Schoer, 1984; Gosselin et al., 1984). Without treatment, the average dose may result in death within 10-12 days, but death within 8-10 hours has also been reported (WHO, 1996). It has been suggested that children may be more sensitive than adults to thallium toxicity (Kazantzis, 1994); however, there are reports of thallium used therapeutically in which children tolerated larger doses than adults (WHO, 1996; citing Ormerod, 1928; Sessions and Goren, 1947; Prick, 1979).

Numerous case studies involving thallium poisoning have been reported in the literature, and are summarized in WHO (1996) and U.S. EPA (1992a and b). In cases of severe poisonings, victims have shown increasing tachycardia, progressive hypotension, weakened reflexes and peripheral cyanosis. Lower lethal doses cause gastroenteritis, salivation, nausea and vomiting. Within two

to five days, neurological disorders become apparent. Within five to seven days, hallucination, lethargy, delirium, convulsions, tingling pain in the extremities and muscular weakness are followed by coma. Death is caused by respiratory failure or cardiac arrest (WHO, 1996). In less severe cases of thallium intoxication, poisoning initially causes acute gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea, abdominal pain). Neurological effects develop hours to days later with symptoms including insomnia, excessive thirst, psychological changes, neuralgic pains especially in the soles, and a combination of motor and sensory neuropathies. Later on, hypertension and tachycardia are frequently observed. Alopecia, the most characteristic sign of thallium poisoning, occurs approximately two weeks post-ingestion. Atrophic changes of the skin can occur. White 'lunula' bands can be seen on the nails of fingers and toes. Mental disturbances can occur, including psychosis, paranoia and hallucinations. After four to five weeks, survival is likely but recovery may take several months. Some neurological and mental disturbances may persist (WHO, 1996; Chang et al., 1996).

Genetic Toxicity

In a recently published report of a man who ingested 200 mg thallium sulfate, it was documented that neither the yield of structural chromosomal alterations or sister chromatid exchanges were significantly altered in peripheral blood lymphocytes. The authors noted, however, that there was a statistically significant increase in binucleated cells with micronuclei, indicating that thallium has the ability to interfere with chromosome distribution during cell division (Hantson et al., 1997).

Developmental and Reproductive Toxicity

WHO (1996) summarizes reviews of more than 20 cases of thallium intoxication during pregnancy. Although low birth weights were reported, no teratogenic effects were documented. Intoxication occurring after the first trimester can induce in the newborn baby some symptoms of acute intoxication seen in adults (i.e., alopecia and lunular stripes in the nails). A pregnant woman developed alopecia and polyneuritis after ingesting 0.5 g thallium eight weeks before term. Although her baby was relatively underweight, it had developed normally *in utero* and there were no signs of thallium poisoning. Ingestion of 1.2 g thallium by a woman two days before giving birth caused the death of her newborn baby.

A retrospective study was conducted to examine the incidence of congenital malformations in a population exposed to thallium emissions from a cement plant (Dolgner et al., 1983). The authors reported that the rate of malformations in the exposed group did not exceed the expected rate for the general population. The degree of maternal exposure to thallium could not be ascertained.

Noncancer Chronic Toxicity

Studies of chronic thallium exposure resulting in poisoning have been summarized by several authors; however there is no information regarding exposure concentrations (WHO, 1996; citing Buschke and Langer, 1927; Gefel et al., 1970; Schoer, 1984; and Goldblatt, 1989). Symptoms of chronic thallium poisoning include peripheral sensory disturbances, mental changes, weight loss and sleeplessness. In more severe cases, the following have been reported: hair loss, leg pains,

severe polyneuritis with an inability to walk, blindness, cardiac disorders, renal dysfunction, endocrine disorders, psychoses and encephalitis.

Epidemiological investigations have been conducted in a thallium-contaminated area around a cement plant in Germany. Results of three medical surveys between 1979 and 1981 indicate that the majority of the population had significantly elevated urinary thallium concentrations when compared with an unexposed reference population (Dolgner et al., 1983). Positive correlations were found between thallium concentrations in hair and urine samples of exposed people and some symptoms of thallium poisoning (e.g., pain in muscles and joints, sleep disorders, fatigue); however, there was no correlation with certain symptoms which are usually associated with chronic thallium poisoning (e.g., skin disorders, hair loss, lunular stripes in the nails) (WHO, 1996; citing Schoer, 1984; and Brockhaus et al., 1981).

In a limited study of 36 cement plant workers, no correlation was found between neurological deficits and thallium concentrations in blood, urine, and hair samples (Ludolph et al., 1986). Occupational exposure to more than 0.01 mg thallium/m^3 for 16 to 17 years caused disorders of the vascular system, as well as neurological symptoms (Ohnesorge, 1985; as cited by WHO, 1996).

Carcinogenicity

No epidemiological studies examining cancer incidence in relation to thallium exposure were located. In addition, no case reports suggesting a link between thallium exposure and cancer were found.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

There are inadequate quantitative exposure estimates from the case reports and epidemiological studies of adverse human health effects from thallium exposure to establish a dose-response relationship.

Several studies in experimental animals have identified levels of thallium which have resulted in adverse effects; however, in no study is a range of doses tested that demonstrates a clear dose-response relationship between thallium toxicity and administered dose. Therefore, the database is limited for use in risk assessment.

The lowest concentrations of thallium tested were those used in the 90-day subchronic study reported by Stoltz et al. (1986). In this study, Stoltz et al. reported that the only grossly observed finding thought to be treatment-related was alopecia. However, due to the limited evidence of histologic changes seen with light microscopy, Stoltz et al. attributed the alopecia to normal self-barbering or the normal cyclic pattern of hair growth in rodents and concluded that the finding was biologically insignificant. Alopecia is characteristic of thallium toxicity in both animals and humans, and in humans thallium was once used as a depilatory agent. More importantly, it appears that alopecia is part of a continuum of dermal morphological changes and is therefore an early sign of an adverse health effect. OEHHA scientists have reviewed the raw data from the study and concluded that in most cases, the alopecia observed in male rats at all doses, and in female rats at the low and mid doses may have been due to self-barbering or normal pattern of

hair growth as Stoltz et al. reported. However, the finding of two cases of alopecia in the high-dose group for female rats with atrophy of the hair follicles is consistent with the pattern of alopecia from thallium toxicity observed by other investigators. Based on the overall weight-of-evidence for thallium-related alopecia and the two positive findings in female rats at the highest dose, a NOEL of 0.05 mg/kg-day (administered dose equals 0.0405 mg/kg-day) was identified from this study.

In the two studies reported by Downs et al. (1960), rats were administered thallium acetate or thallium oxide in diet for 15 weeks. From these studies a NOAEL and LOAEL of 5 and 15 mg thallium acetate/kg diet were identified, respectively. These studies are limited, however, by the small number of animals in each dose group and the high mortality observed in both treated and control animals. In addition, the exact exposure concentrations were not determined. The authors estimated consumption to be in the range of 0.78-2.34 mg Tl/kg bw-day for the animals administered 15 mg thallium acetate/kg diet. Using default assumptions provided by U.S. EPA, the NOAEL and LOAEL correspond to 0.4 and 1.2 mg Tl/kg bw-day.

There are two studies that examined the effects of thallium sulfate administered in drinking water (Manzo et al., 1983; Formigli et al., 1986). In one study, approximately 1 mg Tl/kg-day for 36 weeks resulted in mild to severe cutaneous disorders, alopecia, and abnormal electrophysiological parameters in rats. In the other study, approximately 0.74 mg Tl/kg-day for 60 days resulted in adverse effects on sperm motility and maturation in rats. Although effect levels are identified in these studies, they are higher than those observed in the Stoltz et al. (1986) study. In addition, they are not true LOAELs. These studies are greatly limited in that each was performed at only one dose level, consequently they do not allow the evaluation of a dose-response relationship.

Herman and Bensch (1967) found histopathological changes in kidney, liver and brain in rats dosed subcutaneously with thallium. However, uncertainty in the dosing protocol, the relatively high levels of thallium administered in each dose, and difficulties in extrapolating between subcutaneous and oral administration make this study unsuitable for derivation of a PHG.

It is also important to note that in studies of thallium exposure in humans, symptoms of peripheral sensory disturbances, mental changes, weight loss and sleeplessness occurred in poisoning incidents that were less severe than those that produced alopecia in rodents.

OEHHA scientists conclude that the study by Stoltz et al. (1986) provides the most sensitive indication in the available literature of the toxicity of thallium, and is the most appropriate study for the derivation of the PHG. In establishment of the federal MCL and MCLG for thallium, U.S. EPA also selected the Stoltz et al. (1986) study as the most appropriate for deriving guidance values for drinking water. However, based on the absence of histopathological changes in the hair follicles, U.S. EPA identified the highest dose (0.2 mg/kg-day) as a NOAEL.

Carcinogenic Effects

No studies on the carcinogenicity of thallium were located either in animals or humans. In the absence of information, no dose-response assessment for carcinogenic effects can be made.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, as well as for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Calculation of a public health-protective concentration (C, in mg/L) for thallium in drinking water follows the general equation for noncarcinogenic endpoints:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL/LOAEL	=	No-observed-adverse-effect-level or lowest-observed-adverse-effect-level
BW	=	Adult body weight
RSC	=	Relative source contribution
UF	=	Uncertainty factors
L/day	=	Daily water consumption rate

For thallium, a NOEL of 0.0405 mg/kg-day was identified from a 90-day drinking water study in rats (Stoltz et al., 1986). The default for adult human body weight is 70 kg for a male. A default value of 20% was used for the relative source contribution, since food is likely to provide a greater contribution to exposure than drinking water. The human daily water consumption default value is 2 L/day for adults. A cumulative uncertainty factor of 3,000 is applied to account for use of a subchronic study (10), interspecies extrapolation (10), intraspecies variation (10), and a modifying factor for the steep dose-response curve (3). It is important to note that in the study reported by Manzo et al. (1983), a dose level of approximately 1 mg/kg-day in drinking water for 36 weeks resulted in 21% mortality, as well as cutaneous disorders including alopecia. A dose of 1 mg/kg-day is only 25 times higher than the NOEL identified in the Stoltz, et al. (1986) study.

Therefore,

$$C = \frac{0.0405 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{3{,}000 \times 2 \text{ L/day}}$$

$$= 0.0000945 \text{ mg/L}$$

$$= 0.001 \text{ mg/L (rounded to one significant figure)}$$

$$= 0.1 \text{ µg/L or } 0.1 \text{ ppb}$$

Based on this calculation, OEHHA has derived a PHG of 0.1 µg/L (0.1 ppb) for thallium in drinking water.

RISK CHARACTERIZATION

The Stoltz et al. (1986) study was used for the derivation of the PHG since it identified a possible toxic effect of thallium at lower concentrations than any of the other studies. However, the study is limited by the short exposure duration (90 days). The raw data indicate that the incidence of severe alopecia (ratings of 4 or 5 out of 5) was due to self-barbering in all but two cases. For the two cases observed at the highest dose level in female rats, histopathological analysis did not reveal anything more biologically significant than what would be expected during normal cyclic hair growth in rodents. The sporadic occurrences of minor alopecia (about 10 days or less with a rating of 1 out of 5) also appeared to be the result of the normal cyclic pattern of hair growth. The incidences of shedding, rough coat and piloerection were sporadic and in most cases occurred on only a few days during the course of the study (in many cases, only on one or two days). As for the high frequency of minor to moderate exopthalmos and lacrimation at all dose levels, we conclude these effects are unlikely to be systemic effects considering the usual mechanism of action. Opthalmic examinations did not reveal any dose-related abnormalities. If exopthalmos and lacrimation occurred via inhalation, it might have been related to the sulfate salt of thallium used in this study. It should be noted that all of these endpoints are visual (qualitative) and are subject to the interpretation and variation of the examining technicians.

Based on case reports and epidemiological studies in humans, there does not seem to be sufficient data to suggest that infants or pregnant women are more sensitive to the effects of thallium than the general population. Data regarding concentrations of thallium which are toxic in children are contradictory. However, the available data are inadequate to fully assess these subpopulations. In addition, reproductive and developmental effects have been observed in animal studies. Because thallium is eliminated in both urine and feces, any subpopulations with diminished excretory function may be at increased risk of thallium toxicity. It is considered that the UF of 10-fold to account for human variability should be adequate to protect potentially sensitive subpopulations.

The World Health Organization's "Task Group on Environmental Health Criteria for Thallium" concluded that, due to uncertainties in the database, it was not possible to recommend a health-based exposure limit. In reviewing the animal data, including the study by Stoltz et al. (1986), the Task Group noted that, "...it appears that an intake of 0.01 mg/kg per day may be associated with adverse effects. No doses lower than this have been tested." The Task Group also stated that until better information on the dose-response relationship comes available, it seems prudent

to keep exposures at levels that lead to urinary concentrations of less than 5 μg/L. The estimated daily oral intake corresponding to urinary thallium concentrations of 5 μg/L is approximately 10 μg thallium in the form of a soluble compound (WHO, 1996).

There are additional sources of uncertainty in the development of the PHG for thallium that are the general issues of uncertainty in any risk assessment, particularly inter- and intra-species extrapolation and relative source contribution (RSC). For PHGs, our use of the RSC has, with few exceptions, followed U.S. EPA drinking water risk assessment methodology. The RSC range is 20% to 80% (0.2 to 0.8) depending on the scientific evidence. In the derivation of a PHG for thallium, a RSC of 20% was selected. In the general population, environmental exposure to thallium does not pose a health threat. The majority of intake comes from foodstuffs, with drinking water and air generally contributing very small amounts of thallium (WHO, 1996). Therefore, a default value of 20% was used.

OTHER REGULATORY STANDARDS

U.S. EPA has established a Maximum Contaminant Level Goal (MCLG) of 0.0005 mg/L for thallium and a Maximum Contaminant Level (MCL) of 0.002 mg/L, based on the 90-day gavage study in rats (Stoltz et al., 1986). In this study, the only grossly observed finding at necropsy thought to be treatment-related was alopecia; however, based on the absence of light microscopic histopathologic changes, U.S. EPA identified a NOAEL of 0.2 mg/kg-day. Due to uncertainties in the NOAEL, U.S. EPA incorporated a 3000-fold uncertainty factor (10 for use of a subchronic study, 10 for intra-species variability, 10 for interspecies variability, and 3 to account for inadequate testing of other endpoints of toxicity.) Based on this NOAEL, a Drinking Water Equivalent Level (DWEL) of 2.45 μg Tl/L was calculated, rounded to 2 μg Tl/L. The federal MCL is the same as the DWEL, and expressed as 0.002 mg/L. The MCLG incorporates a Relative Source Contribution (RSC) of 20%. The current California MCL is also 0.002 mg/L (2 ppb).

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